

Report of 337 Patients With Renal Cell Carcinoma Emphasizing 110 With Stage IV Disease and Review of the Literature

PATRICK GUINAN, MD,^{1,2,3*} DAVID STUHLBREHER, MD,^{1,2} WALTER FRANK, MD,^{1,2} AND MARVIN RUBENSTEIN, PhD^{1,3,4}

¹Division of Cellular Biology, Hektoen Institute for Medical Research, ²Department of Urology, University of Illinois College of Medicine, ³Department of Urology, Rush Presbyterian St. Lukes Medical Center, and ⁴Department of Biochemistry, Rush Presbyterian St. Lukes Medical Center, Chicago, Illinois

Background: In the literature, the interdependence of variables, including stage, sex, age, tumor size, therapy, and survival, is complex. The size variable has heretofore received relatively little emphasis.

Method: This was a retrospective evaluation of 337 patients with kidney cancer treated at the University of Illinois Affiliated Hospitals. Data were collected on stage, sex, age, tumor size, TNM stage, therapy, and survival. Statistical analyses included Kaplan-Meier 5-year survivals, as well as multivariate analysis utilizing the Cox regression model. A subset of 110 patients with TNM Stage IV disease is further evaluated employing a multivariate analysis. The principal form of therapy was nephrectomy.

Result: Five-year survivals by stage varied from 100% for Stage I, 96% for Stage II, 59% for Stage III, to 16% for Stage IV. In the subset of 110 patients with TNM Stage IV disease, those with a single metastasis had better survivals than those with two or more. Those having nephrectomy had better survivals ($P < 0.05$). Therapy (in addition to nephrectomy) was curative (defined as cytotoxic chemotherapy or immunotherapy) in 40 patients and palliative (defined as radiation to bone metastases, hormone therapy, or supportive) in 70 patients. Multivariate analysis of TNM Stage IV variable differences indicated that only tumor size differences and nephrectomy significantly affected survival.

Conclusions: Of importance is the observation that among these patients, survival is directly correlated with tumor size.

J. Surg. Oncol. 64:295–298, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: kidney cancer; tumor size; tumor variables; survival

INTRODUCTION: INCIDENCE OF RENAL CELL CARCINOMA

The 1996 estimate for new cases of renal cell carcinoma (ACC) in the United States was 30,600, with an estimated 12,000 deaths from this cancer [1]. To better define the natural history of this malignancy, we review our experience in treating 337 patients with the disease at University of Illinois Affiliated Hospitals. Since TNM Stage IV disease has a particularly ominous prognosis, we analyzed these 110 patients more critically.

MATERIALS AND METHODS

This was a retrospective evaluation of 337 patients with kidney cancer treated at the University of Illinois Affiliated Hospitals, which include the University of Illinois and the Cook County, Michael Reese-Humana,

*Correspondence to: Patrick Guinan, Division of Cellular Biology, Hektoen Institute for Medical Research, 627 S. Wood St., Chicago, IL 60612.
Accepted 21 December 1996

TABLE I. Prognostic Variables for Survival in 337 Patients With Renal Cell Carcinoma

| Patient characteristics | No. of patients (%) | 5-year survival | Significance |
|-------------------------|---------------------|-----------------|--------------|
| Sex: | | | |
| Male | 216 (64) | | |
| Female | 121 (36) | | |
| Age: | | | |
| Mean | 58.7 yrs | 57 | |
| 0–39 | 32 (10) | 42 | |
| 40–49 | 52 (15) | 68 | |
| 50–59 | 88 (26) | 59 | |
| 60–69 | 101 (30) | 48 | |
| 70–79 | 52 (15) | 73 | |
| Over 79 | 12 (4) | 69 | |
| Size (cm) | | | |
| <2.5 | 15 (4) | 100 | $P < 0.05$ |
| 2.5–4.9 | 56 (16) | 84 | |
| 5.0–7.4 | 87 (26) | 61 | |
| 7.5–10.0 | 75 (22) | 51 | |
| >10.0 | 104 (32) | 27 | |
| TNM stage: ^a | | | |
| I | 12 (4) | 100 | $P < 0.05$ |
| II | 81 (24) | 96 | |
| III | 134 (40) | 59 | |
| IV | 110 (32) | 16 | |
| Nephrectomy: | | | |
| Yes | 288 (86) | | |
| No | 49 (14) | | |

^aAmerican Joint Committee on Cancer staging.

and Westside Veterans Administration hospitals. Of these patients, 110 had TNM Stage IV disease. Only those patients with renal adenocarcinoma were included; transitional cell carcinomas, Wilm's tumors, and sarcomas were excluded.

Data were collected on stage, sex, age, tumor size, TNM stage, therapy, and survival. Statistical analyses included Kaplan-Meier 5-year survivals as well as multivariate analysis utilizing the Cox regression model.

RESULTS

All Patients

A total of 337 patients with a histologic diagnosis of RCC were evaluated (Table I). There were 216 (64%) male and 121 (36%) female patients. The average age of the patients was 58.7 years, with a range of 7–95 years. There were 32 (10%) patients <40 years old, 52 (15%) between 40–49, 88 (26%) between 50–59, 101 (30%) between 60–69, 52 (15%) between 70–79, and 12 (4%) >79 years. There were 15 (4%) patients with tumors <2.5 cm., 56 (16%) with tumors 2.5–4.9 cm., 87 (26%) with tumors 5.0–7.4 cm., 75 (22%) with tumors 7.5–10.0 cm., and 104 (32%) patients with tumors >10.0 cm ($P < 0.05$). Twelve (4%) patients had TNM Stage I disease, 81 (24%) had Stage II, 134 (40%) had Stage III, and 110 (32%) had Stage IV ($P < 0.05$). The principal form of

therapy was nephrectomy, which was performed in 288 (86%) of the 337 patients. The 49 patients who did not undergo nephrectomy, in general, had Stage IV disease. Five-year survivals by stage varied from 100% for Stage I, 96% for Stage II, 59% for Stage III, to 16% for Stage IV.

Subset of 110 Patients With M+ Disease

There were 110 patients with TNM Stage IV disease (Table II). There were 73 (66%) male patients and 37 (34%) female patients. Fifty-one (46%) were patients 59 years or less and 59 (54%) were older than 59. There were 53 (49%) patients with tumors <10 cm and 57 (51%) with tumors 10 cm or greater ($P < 0.01$). Sixty-two (56%) patients had a nephrectomy and 48 (44%) did not ($P < 0.001$). Patients with a single metastasis had better survivals than those with two or more. Those having nephrectomy had better survivals ($P < 0.05$). Therapy (in addition to nephrectomy) was curative (defined as cytotoxic chemotherapy or immunotherapy) in 40 patients and palliative (defined as radiation to bone metastases, hormone therapy, or supportive) in 70 patients.

Multivariate analysis of TNM Stage IV variable differences indicated that only tumor size differences and nephrectomy significantly affected survival (Table III).

TABLE II. Prognostic Variables for Survival of a Subset Consisting of 110 Patients With TNM* Stage IV Disease

| Variable | No. of patients (%) |
|--------------|---------------------|
| Sex: | |
| Male | 73 (66) |
| Female | 37 (34) |
| Age: | |
| 0–34 | 8 (7) |
| 35–39 | 3 (3) |
| 40–49 | 11 (10) |
| 50–59 | 29 (26) |
| 60–69 | 40 (37) |
| 70–79 | 12 (11) |
| >79 | 7 (6) |
| Size (cm): | |
| <2.5 | 2 (2) |
| 2.5–4.9 | 11 (11) |
| 5.0–7.4 | 15 (14) |
| 7.5–9.9 | 25 (23) |
| 10 or > | 57 (52) |
| Nephrectomy: | |
| Yes | 62 (56) |
| No | 48 (44) |
| Therapy: | |
| Chemo- | 33 (30) |
| Immuno- | 7 (7) |
| Radiation | 25 (23) |
| Hormone | 14 (13) |
| Supportive | 31 (28) |

*American Joint Committee on Cancer staging.

TABLE III. Probability of Survival of 110 Stage IV Patients

| Variables | χ^2 | P |
|-------------|----------|-----|
| Sex | .0016 | NS |
| Age | 1.02 | NS |
| Tumor size | 4.14 | .05 |
| Nephrectomy | 5.17 | .02 |
| Therapy | 3.06 | NS |

NS = not significant.

DISCUSSION

Renal cell carcinoma was the twelfth leading cause of cancer death in Illinois [2] in 1991. Among urologic cancer deaths, kidney cancer now exceeds bladder cancer and is second only to that of the prostate [1].

Numerous articles [3–17] have described aspects of renal cell carcinoma that influence survival. From a review of this literature on prognostic variables in RCC, among the numerous parameters that have been considered, several stand out (Table IV). These include stage and grade, as well as vessel, capsular, nodal, and metastatic involvement. Mentioned less often are sex, age, and cell type. Therapy has been relatively less important because for localized disease (TNM Stages I, II, III), nephrectomy is the standard therapy and for disseminated disease (TNM Stage IV), no therapy is considered effective. Tumor size, given the spherical nature of RCC and the good imaging techniques, is conspicuous in the

fact that it is mentioned so infrequently. It is of interest that those authors that commented on variables that they felt were unimportant often cited parameters, e.g., venous involvement [6,7,10,12], that other writers considered to be significant [4,9,13].

The present retrospective series confirms the findings of numerous prior reviews [18–22] with respect to many of these variables. Age and sex as prognostic factors have been noted to be both important [3,10,16] and unimportant [9,11]. The average age of a patient with kidney cancer is the late fifties, being approximately twice as common in males. A review of the literature reveals that stage was the most important prognostic variable. At presentation the most common stage noted was Stage III and the next most frequently seen was Stage IV. The present series had slightly more patients with Stage II and III disease than the other reviews. All series indicated a decrease in survival rates with increasing stage. The survival rate for Stage IV disease is uniformly poor. These trends were reflected in the present series.

What is noteworthy about the present series is the contribution of tumor size as a survival variable. Although some authors [3,4,12,14] have observed that size correlated with survival, others have not noted this relationship [7,9,11,15]. In this series of 337 patients, there was a significant inverse relationship between tumor size and survival. Patients with larger tumors had poorer survivals.

TABLE IV. Prognostic Variables of Renal Cell Carcinoma

| Author [ref] | Year | Pts. | Useful | Not useful |
|--------------------------|------|------|---|--|
| Grabstald [3] | 1966 | — | Cell type, size vessel and capsule involvement, female sex, and age | |
| Bottiger [4] | 1970 | 100 | Stage, grade, metastases, elevated sedimentation rate, size, and invasion of renal vein | |
| Skinner et al. [5] | 1971 | 309 | Stage, grade, perinephretic fat and nodal involvement | Presenting symptoms and laboratory tests |
| DeKernion & Berry [6] | 1980 | — | Nodal, renal capsule or contiguous organ involvement, metastasis, and grade | Venous involvement |
| Fuhrman et al. [7] | 1982 | 103 | Nuclear grade, stage, and cell type | Size, venous involvement, and tumor pattern |
| Jones [8] | 1982 | — | Stage and cell type | — |
| Sufrin [9] | 1982 | — | Stage, grade, venous and nodal involvement, and male sex | Cell type, size, age, and classic triad |
| Selli et al. [10] | 1983 | 115 | Grade, metastases, local extent of tumor, age, and weight loss | Venous involvement, sex, and race |
| Nurmi[11] | 1984 | 257 | Metastases, nodal involvement and grade | Direct extension of tumor, cell type, size, sex, and age |
| Golimbu et al. [12] | 1986 | 326 | Capsular, nodal, or perirenal fat involvement, and size | Venous involvement |
| DeKernion & Mukamel [13] | 1987 | — | Venous, nodal or perinephretic fat involvement, and grade | Size significant as related to adenoma vs carcinoma |
| Medeiros et al. [14] | 1988 | 121 | Nuclear grade, stage, cell type, and size | |
| Reis & Faria [15] | 1988 | 200 | Histologic pattern | Size and grade |
| Storkel et al. [16] | 1990 | 632 | Stage, nuclear grade, cell type, growth pattern, and age | |
| Dinney et al. [17] | 1992 | 314 | Stage, nodal involvement, metastases, and cell type | |

Survival of Stage IV disease is particularly unfavorable. In general, neither age, sex, nor therapy influenced survival. However, tumor size and nephrectomy did influence survival. Size has not been commented upon specifically for Stage IV disease. Nephrectomy was performed either for pain and/or bleeding, or in the remote hope of a spontaneous regression. Nephrectomy may have benefited survival for a variety of reasons, including selection bias, spontaneous regression, and/or reduction in tumor burden. However, in this series it, as well as nephrectomy, did appear to influence survival.

There are many potential prognostic variables in RCC. Their interrelationship is complex and how dependent or independent any one is on any other is at times difficult to understand. Stage is the most commonly employed prognostic variable in clinical practice, because it allows urologists to select therapy based upon historical survival data following treatment of tumors of defined anatomic spread. Since tumor size is a precise definition of anatomic spread, perhaps it should be factored into staging systems.

In summary, renal cell carcinoma is a malignancy of clinical importance. Survival is correlated with TNM Stage. Of importance to the treating clinician is the currently underemphasized observation that size is also correlated to survival and may possibly be employed as a predictor in making management decisions.

ACKNOWLEDGMENTS

This work was funded in part by the Blum-Kovler Foundation (Chicago, IL) and the Cancer Federation (Banning, CA).

REFERENCES

1. Parker SL, Tong T, Bolden S, Wingo PA: Cancer statistics. *CA Cancer J Clin* 1996;46:5-27.
2. American Cancer Society: Cancer in Illinois: 1991: An incidence report by 111 hospitals. American Cancer Society, Illinois Division, 1992.
3. Grabstald H: Renal-cell cancer. *CA Cancer J Clin* 1996;16:102-110.
4. Bottiger LE: Prognosis in renal carcinoma. *Cancer* 1970;26:780-787.
5. Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF: Diagnosis and management of renal cell carcinoma: A clinical and pathologic study of 309 cases. *Cancer* 1971;28:1165-1177.
6. DeKernion JB, Berry D: The diagnosis and treatment of renal cell carcinoma. *Cancer* 1980;45:1947-1956.
7. Fuhrman SA, Lasky LC, Limas C: Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol* 1982;6:655-663.
8. Jones GW: Renal cell carcinoma. *CA Cancer J Clin* 1982;35:280-285.
9. Sufrin G: The challenge of renal cell adenocarcinoma. *Surg Clin N Am* 1982;62:1101-1118.
10. Selli C, Hinshaw W, Woodard B, Paulson D: Stratification of risk factors in renal cell carcinoma. *Cancer* 1983;52:899-903.
11. Nurmi M: Prognostic factors in renal carcinoma: An evaluation of operative findings. *Br J Urol* 1985;56:270-275.
12. Golimbu M, Joshi P, Sperber A, Tessler A, Al-Askari S, Morales P: Renal cell carcinoma: Survival and prognostic factors. *Urology* 1986;27:291-301.
13. DeKernion JB, Mukamel E: Selection of initial therapy for renal cell carcinoma. *Cancer* 1987;60:539-546.
14. Medeiros J, Gelb A, Weiss L: Renal cell carcinoma: Prognostic significance of morphologic parameters in 121 cases. *Cancer* 1988;61:1639-1651.
15. Reis M, Faria V: Renal carcinoma: Reevaluation of prognostic factors. *Cancer* 1988;61:1192-1199.
16. Storkel S, Thoenes W, Jacobi GH, Engelmann U, Lippold R: Prognostic parameters of renal cell carcinoma. *Eur Urol* 1990;18:36-37.
17. Dinney CP, Awad SA, Gajewski JB, Belitsky P, Lannon SG, Mack FG, Millard OH: Analysis of imaging modalities, staging systems, and prognostic indicators for renal cell carcinoma. *Urology* 1992;39:122-129.
18. Patel N, Lavengood R: Renal cell carcinoma: Natural history and results of treatment. *J Urol* 1978;119:722-726.
19. Waters W, Ritchie J: Aggressive surgical approach to renal cell carcinoma: A review of 130 cases. *J Urol* 1979;122:306-309.
20. Boxer R, Waisman J, Lieber MM, Mampaso FM, Skinner DG: Renal carcinoma: Computer analysis of 96 patients treated by nephrectomy. *J Urol* 1979;122:598-601.
21. Katz SA, Davis JE: Renal adenocarcinoma: Prognostics and treatment reflected by survival. *Urology* 1977;10:10-11.
22. Robson CJ, Churchill BM, Anderson W: The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1969;101:297-301.